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CONCISE COMMUNICATION

Review of 52 cases with Hailey–Hailey disease identified 25 novel mutations in Chinese Han population

Zhe WANG,[1,2] Lulu LI,[2] Lele SUN,[2] Zihao MI,[2] Fanghui FU,[1] Gongqi YU,[2] Xian FU,[2] Hong LIU,[1,2] Furen ZHANG[1,2]

[1]*Shandong Provincial Hospital for Skin Diseases, Shandong University,* [2]*Shandong Provincial Hospital for Skin Diseases and Shandong Provincial Institute of Dermatology and Venereology, Shandong First Medical University and Shandong Academy of Medical Sciences, Jinan, China*

ABSTRACT

Hailey–Hailey disease (HHD) is a rare autosomal dominant inherited keratosis caused by mutations in *ATP2C1*. The aim of our study was to identify and analyze the features of the mutations in HHD. We examined 52 Chinese Han cases which were diagnosed as HHD based on their clinical and histological findings. Genomic DNA polymerase chain reaction and direct sequencing of *ATP2C1* were performed from peripheral blood samples of the patients and 100 unrelated healthy controls. Twenty-five novel mutations and 14 recurrent mutations were identified, including 11 (28.2%) missense mutations, nine (23.1%) frame-shift deletion mutations, eight (20.5%) nonsense mutations, seven (17.9%) splicing mutations and four (10.3%) frame-shift insertion mutations. Together with ours, all 209 mutations showed a uniform distribution without hotspots or clusters. In addition, there is no specific genotype–phenotype correlation in HHD. Our findings update the spectrum of mutations in *ATP2C1*.

Key words: *ATP2C1*, Hailey–Hailey disease, mutation analysis, novel mutations, Sanger sequencing.

INTRODUCTION

Hailey–Hailey disease (HHD; Online Mendelian Inheritance in Man #169600), also known as familial benign chronic pemphigus, is a rare autosomal dominant inherited keratosis caused by dysfunction of Ca^{2+} signal transduction in keratinocytes. In HHD, recurrent pruritic vesicles and painful erosion with crusts occur on the friction and flexure areas, especially axillae and groin.[1] Mutations in *ATP2C1* have been implicated in the pathogenesis of HHD. To date, 184 mutations in *ATP2C1* have been identified.[2–7]

CASE REPORT

We report here the research for identifying and analyzing underlying mutations of *ATP2C1* in 52 Chinese Han patients. All patients were diagnosed with HHD based on their clinical and histological findings, including 35 male and 17 female patients. The ages ranged 10–72 years. Twenty-nine of them had a family history while 16 patients were sporadic (Table S1).

With ethical committee approval and patient informed consent, genomic DNA was extracted from peripheral blood samples of the patients and 100 unrelated healthy controls. Twenty-seven pairs of primers (Table S2) were designed to amplify 28 exons including intron boundaries by polymerase chain reaction. The products were directly sequenced with an ABI 3500 xL Genetic Analyzer (Applied Biosystems, Waltham, MA, USA).

DISCUSSION

In total, we identified 25 novel mutations (Fig. 1) and 14 recurrent mutations, including 11 (28.2%) missense mutations, nine (23.1%) frame-shift deletion mutations, eight (20.5%) nonsense mutations, seven (17.9%) splicing mutations and four (10.3%) frame-shift insertion mutations (Fig. S1). None of the novel mutations were detected in 100 healthy controls or found in the three public variation databases (1000 Genomes Project, HapMap and Exome Aggregation Consortium).

ATP2C1 encodes the human secretory pathway Ca^{2+}/Mn^{2+}-ATPase protein 1 (SPCA1), which consists of an actuator domain (A), a nucleotide-binding domain (N), a phosphorylation domain (P) and 10 transmembrane domains (M1–M10).[8] Thirty-nine mutations identified in the present study had a dispersed distribution throughout the SPCA1 protein (Fig. 1). Up to now, including the mutations we identified in this study, a total of 209 mutations in *ATP2C1* have been found. However, all of

Correspondence: Furen Zhang, M.D., Ph.D., and Hong Liu, M.D., Ph.D., Shandong Provincial Institute of Dermatology and Venereology, Shandong First Medical University, 27397 Jingshi Road, Jinan, Shandong Province 250022, China. Emails: zhangfuren@hotmail.com (F. Z.); hongyue2519@hotmail.com (H. L.)
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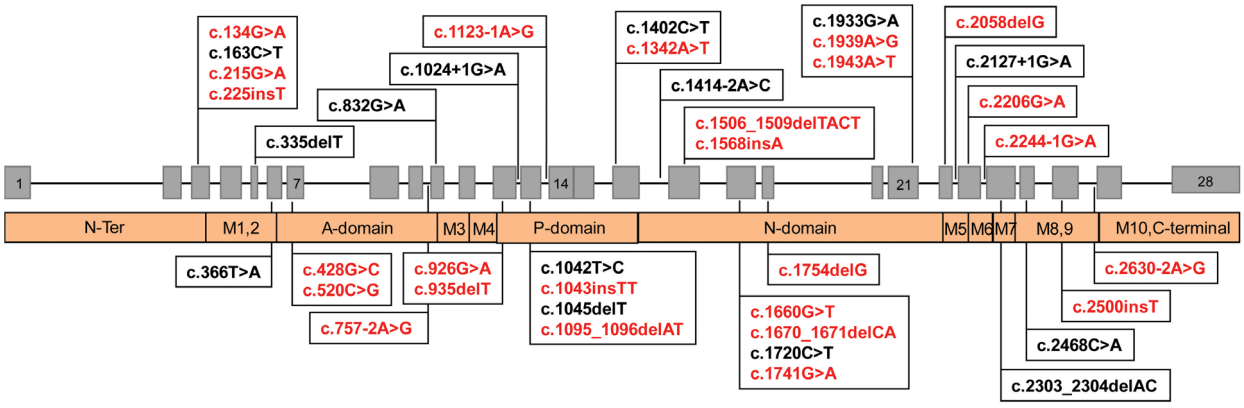

Figure 1. Schematic representation of *ATP2C1* gene mutations found in our Hailey–Hailey disease patient samples. Red markings denote novel mutations. All *ATP2C1* mutations are described according to the *ATP2C1* isoform 1a (NM_001001487.1, NP_001001487.1).

them followed a uniform distribution without hotspots or clusters, which is consistent with previous investigations.[8]

Along with our findings, 6.2% (13/209) of mutations were in the N-terminus/S1 domain. The N-terminus contained a Ca^{2+}-binding EF hand-like motif which seemed to regulate ion affinity.[9] Mutations in this region may influence the ion affinity and transportation.[10] Of the mutations, 11.0% (23/209) have been identified in M4 and M6 domains. The conserved residues in these two regions were regarded as the Ca^{2+} and Mn^{2+} binding associated functional sites.[11] Thirty-six of the 209 mutations (17.2%) in the cytoplasmic linkage areas (S1–S7), which are flexible helices that contribute to ion transportation, may disorder ion transportation and then cause the clinical phenotype.[10] In addition, there were 6.7% (14/209) mutations found in the A domain, which may damage the regulatory function and thus influence the phosphatase step.[12] Twenty-four of the 209 mutations (11.5%) were in P-domain coding areas and may disrupt the catalytic phosphorylation.[13] Twenty-nine of the 209 mutations (13.9%) were identified in the N-domain. These mutations may affect the nucleotide binding of *ATP2C1* thus causing the dysfunction of the protein. Furthermore, research has shown that any site or type of *ATP2C1* mutation could disrupt the Ca^{2+} homeostasis in Golgi and cause the development of HHD.[6]

We did not find any mutation in 13 patients (25%), and the ratio was similar to the published work.[14] The reason may be that the causal mutations were in the areas that we did not detect, such as introns, non-coding regions or promotor regions. Further whole-exome sequencing is also needed to find whether there is another unknown gene related to HHD.

In 2016, Micaroni *et al*.[8] reviewed all of the reported mutations of HHD since 2000, including 219 independent families and sporadic patients, but failed to find any specific relationships between genotypes and phenotypes. Xu *et al*.[4] summarized all 90 variants in a Chinese Han population. Taking our findings into account, no relationships between genotypes and phenotypes in a Chinese population was found. Multiple phenotypic mutation suggests the impact of other modifying genes.[3]

In conclusion, we report 25 novel mutations and 14 reported mutations in 52 cases. Our findings update the spectrum of *ATP2C1* mutations and may provide help with genetic diagnosis for other family members of the probands. More research is needed to elucidate the function of *ATP2C1* mutations in HHD.

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CONFLICT OF INTEREST: None declared.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1. ATP2C1 potentially pathogenic mutations identified in individuals with HHD.

Figure S1. The sequencing of 25 novel mutations identified in 52 HHD pedigrees.

Table S2. 27 pairs of primers of ATP2C1.